REMARKS

I. Amendments to the Claims

Claim 23 has been amended to clearly define the subject matter of the invention by deleting 'sensitive to thalidomide' and adding 'to inhibit angiogenesis in said tumor,' as proposed by the Examiner at a telephonic interview on March 10, 2008. No new matter has been added.

Claims 1-22, 24, 32, 41-58 and 63-70 were canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

Claims 23, 25-31, 33-40, 59-62 and 71-72 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

II. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A personal interview with Patent Examiner James D. Anderson, Dr. Robertson-Chow, and Ms. Yeah-Sil Moon, attorney for Applicant, was held on March 7, 2008. Also a telephonic interview with the Examiner and Ms. Moon followed on March 10, 2008. Applicant appreciates the Examiner interview and the courtesy of the March 10th call.

During the in-person interview, the Examiner and attorney for Applicant discussed the pending § 112 enablement rejection. Attorney for Applicant pointed out that the pending claims are enabled based on the Examples and descriptions in the specification. Attorney for Applicant presented articles published after the filing date of the application as evidence that a skilled person in the art can practice the claimed invention without undue experimentation based upon the disclosure of the specification. The articles report that inhibition of angiogenesis by thalidomide was discovered by the present inventor, and that thalidomide is now believed to be used for treating blood-borne tumors (*e.g.*, multiple myeloma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), plasma cell leukemia (PCL), hairy cell leukemia (HCL), mantle cell lymphoma (MCL), non-Hodgkin's lymphoma (NHL) and angioimmunoblastic T-cell lymphoma).[1] The Examiner stated that he would discuss the claims and presented articles with Supervisory Examiner Ardin Marschel.

The Examiner called Ms. Moon on March 10, 2008, and proposed amending claim 23 by

[1] Applicant notes that thalidomide is currently approved by the U.S. FDA for treating multiple myeloma and Erythema Nodosum Leprosum (ENL).

deleting 'sensitive to thalidomide' and by adding 'to inhibit angiogenesis in said tumor' per his discussion with Supervisory Examiner Marschel. The Examiner stated that the pending § 112 enablement rejection would be overcome by the proposed amendment and articles presented for treating blood-borne tumors using thalidomide. Attorney for Applicant noted that she would submit an amendment to the claims as proposed and articles discussed at the interview. Applicant's arguments and evidence are discussed below and presented herewith.

III. Arguments and Response to Rejections

The Claimed Invention Meets Enablement Requirements

Claims 23, 25-31, 33-40, 59-62 and 71-72 are rejected under 35 U.S.C. §112 as failing to comply with the enablement requirement. (Pages 3-14 of Office Action). Applicant respectfully traverses the rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (Manual of Patent Examining Procedure ("MPEP") §2164.04, *citing In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claim 23 has been amended by deleting 'sensitive to thalidomide' and by adding 'to inhibit angiogenesis in said tumor', as proposed by the Examiner. The pending claims encompass methods using thalidomide for inhibiting the growth of blood-borne tumors. Applicant respectfully submits that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." (*U.S. v. Telectronics, Inc.*, 857 F.2d at 785).

Applicant respectfully reiterates that the specification adequately enables the pending claims for the reasons provided in the previous response. Specifically, the specification discloses the methods of administering thalidomide to patients having tumors, including mode of administration, dosage forms and formulations (*e.g.*, page 20, lines 2-8, and page 20, line 25 to page 23, line 2, for claims 23, 25, 26, 31, 35, 39, 40, 59-62 and 71), and doses of thalidomide (*e.g.*, page 20, lines 15-24 for claims 27-29 and 36-38). Thus, one skilled in the art would have been able to practice the claimed invention by administering the specified amount of thalidomide

using the specified routes of administration to the specified patients, in accordance with the explicit teachings of the present application.

The specification also discloses working Examples I through III (pages 24-28, chick chorioallantoic membrane (CAM) assay, rabbit cornea angiogenesis assay and inhibition of bFGF induced corneal neovascularization), demonstrating that thalidomide is effective in inhibiting angiogenesis *in vivo*. The inhibition of angiogenesis by thalidomide is described on page 27 of the specification, and Figures 6 and 7. The specification clearly describes that undesired angiogenesis occurs in tumors and the inhibition of undesired angiogenesis halts tumor growth. (*e.g.*, page 2, lines 19-26; page 4, lines 20-27 and page 5, line 1 to page 6, line 3). The Office Action has also recognized that undesired angiogenesis is involved in tumor growth and that thalidomide inhibits angiogenesis in animal models. (Pages 3 and 13 of the Office Action).

Thus, from the description of the specification, one skilled in the art would have been able to appreciate that the inhibition of angiogenesis by administration of thalidomide would lead to the inhibition of the growth of tumors. In view of the foregoing, the specification provides a sufficient guidance as to inhibiting the growth of tumors, by administering an effective amount of thalidomide.

The Office Action acknowledges that the specification enables for *treating multiple myeloma* and inhibiting angiogenesis by thalidomide." (Office Action, pages 5 and 13). Nonetheless, the Office Action alleges that multiple myeloma is the only tumor for which thalidomide has been shown to be effective and one would not reasonably expect thalidomide to be effective in treating any blood borne tumors other than multiple myeloma. (Office Action, pages 4-5). Applicant respectfully disagrees.

In fact, at the interview with attorney for Applicant held on March 7 and 10, 2008, the Examiner stated that the enablement rejection would be overcome by the amendment of the claims proposed by the Examiner and by submitting publications to evidence treatments of the blood-borne tumors using thalidomide.

Applicant herewith submits several articles to support that thalidomide is effective in treating blood-borne tumors[2]. For example, Furman *et al.* (*Abstract #6640*, 2005 and *Abstract* #4835, 2004) report that thalidomide, having anti-angiogenic effects against bFGF and VEGF, is effective in treating patients with chronic lymphocytic leukemia (CLL).

[2] These articles were discussed and submitted to the Examiner at the interview on March 7, 2008. Attached hereto with supplemental IDS and list of references cited. Applicant requests that all these references be made of record in the file history of the application and request the Examiner execute the 1449 form enclosed.

Steins *et al.* (*Blood*, 2002; *Leukemia & Lymphoma,* 2003; and *European Journal of Hematology*, 2007) describe that thalidomide has anti-angiogenic effects and is effective in treating patients with acute myeloid leukemia (AML).

Strupp *et al.* (*Leukemia Research,* 2005) report on study of patients with hairy cell leukemia (HCL) using thalidomide and discuss the role of angiogenesis in the blood-borne tumors.

Wohrer *et al.* (*The Hematology Journal,* 2004) report on effective treatment of plasma cell leukemia with thalidomide and dexamethasone.

Ruan *et al.* (*Abstract* #2751, 2006), Damaj (*Leukemia*, 2003) and Goy (*Clinical Lymphoma & Myeloma,* 2006) describe that targeting angiogenesis is a novel therapeutic strategy in lymphoma, and thalidomide has anti-angiogenic effects and is effective in treating patients with mantle cell lymphoma (MCL).

Game *et al.* (*Abstract* #5235, 2001) report that thalidomide with Vinblastine was effective in treating patients with non-Hodgkin's lymphoma (NHL).

Larson *et al.* (*Clinical Advances in Hematology & Oncology*, 2005) report on effectiveness of thalidomide in patients with HIV-related lymphoma.

Ramasamy *et al.* (*Haematologica*, 2006) report on the study of patients with angioimmunoblastic T-cell lymphoma using thalidomide and dexamethasone.

Folkman (*Nature Review*, 2007) discusses that angiogenesis has an essential role in tumor formation; that understanding angiogenesis process and angiogenesis inhibitors are important for treatments of cancers; and that angiogenesis inhibitor thalidomide was approved for treating multiple myeloma and was being studied for patients with various tumors such as NHL, AML, CLL and leukemias (page 276).

Thomas *et al.* (*Current Opinion in Oncology* 2000) and Brennen *et al.* (*Clinical Prostate Cancer* 2004) also describe that angiogenesis plays an important role in haematological malignancies; that thalidomide has an inhibitory effect on angiogenesis as shown in an animal model by the present inventor D'Amato; and that thalidomide could play a significant role in treating haematological malignancies through anti-angiogenic activity.

Therefore, the evidence provided herein for treating leukemias and lymphomas, together with the evidence provided in the previous response for treating multiple myeloma, establishes the efficacy of thalidomide in treating myeloma, leukemias and lymphomas, the three major classes of blood-borne tumors. These publications evidence that a skilled in the art can use and practice the claimed invention for inhibiting the growth of blood-borne tumors in a human using thalidomide, based on the disclosure of the specification. As such, Applicant respectfully

submits that the inhibition of blood-borne tumors as claimed is adequately enabled in this application, and requests that the rejection be withdrawn.

Further, Applicant noted that the Office Action cites several articles to negate enablement for the claimed invention, alleging that administration of thalidomide to patients having various cancer resulted in no anti-cancer effects. (Pages 3-4 and 8-11).

Applicant respectfully submits that such an alleged teaching does not establish a reasonable basis to question the enablement of the instant claims. At the outset, Applicant respectfully reminds the Examiner that the fact that a reference "teaches away" from a claimed invention is not a proper basis for an enablement rejection. As the Federal Circuit explained, although the question of whether or not a reference "teaches away" from a claimed invention is relevant in determining obviousness, "[it is] not the primary [question] bearing on enablement." (emphasis added). (*Singh v. Brake*, 317 F.3d 1334, 1346, 65 U.S.P.Q.2d. 1641 (Fed. Cir. 2003), the Federal Circuit concluded that the appellant "apparently confused the criteria for proving obviousness with those for demonstrating that a disclosure is nonenabling"). Thus, Applicant respectfully submits that such articles which teach away from the claimed invention can not be the basis of a rejection under §112 because it does not establish a reasonable basis to question the enablement of the instant claims.

Further, although Applicant notes that the articles cited by the Examiner disclosed ineffectiveness of thalidomide against cancer in certain studies[3], the present claims are distinct from those articles. Further, the present specification discloses sufficient guidance to practice the claimed invention for inhibiting the growth of tumors using thalidomide without undue experimentation, unlike those articles published prior to the filing date of this application.

With the response filed on October 31, 2007, Applicant submitted articles which reported that thalidomide had been being studied and used for treating tumors, based on the discovery of the present inventor that thalidomide inhibits angiogenesis. *See, e.g.*, previously submitted Diggle (page 630, left column, the second paragraph); Kumar (page 2478, the second paragraph); Rajkumar (page 900, the last two paragraphs); Singhal *et al.* (page 1565, 2nd paragraph of right column); Kneller A. et al. (page 393, left column); Hideshima T. et al. (page 2943, left column); and Barlogie B. et al. (pages 492-3). The article of the present inventor D'Amato study (*Proc. Natl. Acad. Sci.*, USA 91, 1994, page 4082-5) also describes that thalidomide was effective in inhibiting angiogenesis *in vivo* in rabbit cornea angiogenesis assay, and concludes that there are clear implications for the use of this drug for treating angiogenesis associated diseases including

[3] Applicant makes no admission that such references are enabling, nor any admission as to the contents of their disclosure by this statement.

tumors. *See*, at page 4085.

The publications as a whole confirm (1) that the present inventor demonstrated that thalidomide could be used in inhibiting tumors via inhibiting angiogenesis, (2) that the discovery of the present inventor re-ignited interest in thalidomide against tumors, (3) and that thalidomide is now being used and studied for treatments of various tumors. This art is evidence that a skilled person in the art can practice the claimed invention without undue experimentation based upon the disclosure of the specification.

As to the working examples disclosed in the specification, the Office Action alleges that they are limited to demonstrating the anti-angiogenic activity of thalidomide in animal model of angiogenesis, but there are no *in vitro* or *in vivo* experimental models of any diseases described, including cell proliferation or animal tumor models (Office Action, pages 12-13). Applicant respectfully submits that contrary to the allegations, the provided *in vivo* data reasonably correlates with the claimed invention. As discussed in Applicant's response filed October 31, 2007, Example III of the specification discloses the *in vivo* inhibition of bFGF induced corneal neovascularization by thalidomide. (Specification, pages 26-27). Specifically, the specification discloses that treatment with a dose of 200 mg/kg of thalidomide resulted in an inhibition of the area of vascularized cornea that ranged from 30-51% in angiogenesis assays with a median inhibition of 36%.[4] (Specification, page 27 and Figures 6-7). "[A]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." *In re Brana*, at 1566; MPEP §2164.02. "A rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *See Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985).

Further, the specification clearly describes that blood-borne tumors are associated with angiogenesis and that inhibition of angiogenesis would lead to the inhibition of the growth of blood- borne tumors in humans[5]. (*See also* MPEP §2164.04, *citing in re Marzocchi*, 439 F.2d

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[4] As pointed out in Applicant's response filed October 31, 2007, the rabbit cornea assay of Example III is a well-known and accepted animal model for the determination of a drug's effect on angiogenesis.

[5] Page 5, line 12 to page 6, line 3 of the specification discloses as follows: "It should be noted that angiogenesis has been associated with **blood-born tumors** such as **leukemias**, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the **abnormalities in the bone marrow** that give rise to **leukemia-like tumors**... Therefore, prevention of angiogenesis could lead to the prevention of metastasis of tumors. ..Control of angiogenesis by therapeutic means could possibly lead to cessation of the recurrence of the tumors."

220, 224, 169 U.S.P.Q. 367 (CCPA 1971) (A specification disclosure is "presumptively accurate") (emphasis added))). Indeed, the Examiner himself acknowledges that the working examples demonstrate the anti-angiogenic activity of thalidomide in animal model and the specification enables for treating multiple myeloma (Office Action, pages 5 and 13).

With the response filed on October 31, 2007, Applicant also submitted publications to show the correlation between the methods for inhibition of the growth of tumors in humans and the animal models for angiogenesis inhibition described in the specification. *See e.g.*, Langer *et al.*, Gimbrone *et al.*, "Tumor Growth and Neovascularization: An Experimental Model Using the Rabbit Cornea," *J. Natl. Cancer Inst.* (1974) 52(2): 413-427, and D'Amato *et al.*, "Thalidomide is an Inhibitor of Angiogenesis," *Proc. Natl. Acad. Sci., U.S.A.* (1994) 91: 4082-4085.

Thus, Applicant respectfully submits that the animal model examples in the specification, in effect, constitute working examples for the claimed invention. *In re Brana*, at 1566; MPEP § 2164.02. The Office Action has not provided with any evidence that the examples disclosed in the specification do not correlate with the inhibition of blood-borne tumors in humans. Applicant respectfully reminds the Examiner that "[s]ince the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must...give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required..." (*Id., citing Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985)).

In sum, since the working examples demonstrate inhibition of angiogenesis by thalidomide in animal models and the claims are enabled for treating multiple myeloma, as the Examiner himself acknowledges, and since blood-borne tumors correlate with angiogenesis, Applicant respectfully submits that the pending claims reciting blood-borne tumors are enabled.

Furthermore, Applicant respectfully notes that as well settled, proof of clinical efficacy and human data are not required for purposes of satisfying the enablement requirement. For example, in *In re Brana*, in a manner similar to the Examiner in the present case, the PTO alleged that animal testing was not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Court rejected this argument and stated that "[t]he Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." (51 F.2d at 1567). Moreover, the Court stated that "Title 35 does not demand that such human testing occur within the confines of the Patent and Trademark Office Proceedings." (*Id., citing Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d (B.N.A.) 115 (Fed. Cir. 1994); *see also MPEP §2164* ("[t]he applicant need not demonstrate that the invention is

completely safe.")).

Nonetheless, the Office Action alleges that "[t]he specification provides no direction or guidance for determining the particular administration regimens (e.g. dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans."[6] (Office Action, pages 12-13). Applicant respectfully traverses this rejection.

Applicant respectfully submits that the specification does provide sufficient guidance to enable one of skill in the art to practice the claimed invention. Specifically, dosages, routes of administration, and formulations are provided on page 20 of the instant specification. Applicant respectfully submits that the Examiner appears to be objecting to a screening step. In this regard, Applicant respectfully submits that the screening of compounds is considered a routine practice for one of skill in the art, and such screening is not considered undue experimentation. For example, in *In re Wands*, the Court of Appeals for the Federal Circuit held that claims directed to immunoassay methods were enabled even though in order to practice the claimed methods, one would have to screen "hybridomas to determine which ones secrete antibody with desired characteristics." (858 F.2d at 740). As the Court explained: "[p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." (*Id.*) (emphasis added).

Indeed, the determination by a physician as to whether a compound is effective in treating a disorder is routine and is performed by physicians for every pharmaceutical. Moreover, with regard to screening for effective dosages for the treatment of a disorder in a human, the Board of Patent Appeals and Interferences in *Ex parte Skuballa* stated:

> While some experimentation may be required to determine optimum dosages...such experimentation is not considered undue...We are satisfied that the skilled worker in this art could readily optimize effective dosages and administration regimens... As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplished by simple routine procedures.

(12 U.S.P.Q.2d 1570 (Bd. Pat. App. & Interf. 1989)) (emphasis added).

Thus, to the extent the PTO is basing the rejection under 35 U.S.C. §112 on the need for screening, Applicant respectfully submits that such a rejection is improper. One skilled in the art would have been able to practice the claimed invention by administering the specified amount of thalidomide using the specified routes of administration to patients having blood-borne tumors, as provided on page 20 of the instant specification, and in view of the clear descriptions of the

[6] As discussed, *supra*, the lack of clinical or human data is not a proper basis for an enablement rejection.

relationship between the inhibition of angiogenesis and the tumors in humans in the specification.

The Office Action also alleges that no one drug is used to treat different types of cancer (page 5). Applicant respectfully submits that the contention is not relevant for purposes of satisfying the enablement requirement. Further, as the Examiner is well aware, "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." (MPEP 2164.02, *quoting Gould v. Quigg*, 822 F.2d 1074, 1078, 2 U.S.P.Q. 2d 1302 (Fed. Cir. 1987), *quoting In re Chilowsky,* 229 F.2d 457, 461, 108 U.S.P.Q. 321 (CCPA 1956)). Applicant respectfully submits that the references presented show that thalidomide is effective in treating various types of blood-borne tumors.

In sum, Applicant respectfully submits that the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention, and that to the extent any experimentation is necessary, such experimentation is not undue. Therefore, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Conclusion

Applicant respectfully requests that the above amendments and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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